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Review

Sexual differentiation of human behavior: Effects of prenatal and pubertal organizational hormones

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ABSTRACT

A key question concerns the extent to which sexual differentiation of human behavior is influenced by sex hormones present during sensitive periods of development (organizational effects), as occurs in other mammalian species. The most important sensitive period has been considered to be prenatal, but there is increasing attention to puberty as another organizational period, with the possibility of decreasing sensitivity to sex hormones across the pubertal transition. In this paper, we review evidence that sex hormones present during the prenatal and pubertal periods produce permanent changes to behavior. There is good evidence that exposure to high levels of androgens during prenatal development results in masculinization of activity and occupational interests, sexual orientation, and some spatial abilities; prenatal androgens have a smaller effect on gender identity, and there is insufficient information about androgen effects on sex-linked behavior problems. There is little good evidence regarding long-lasting behavioral effects of pubertal hormones, but there is some suggestion that they influence gender identity and perhaps some sex-linked forms of psychopathology, and there are many opportunities to study this issue.

1. Introduction

Sex matters for human behavior as it does for behavior in other species. Human males and females differ in many ways, including their appearance, their social identity, their social partners, the activities that interest them, how they present themselves to others, their aspirations and values, the likelihood of experiencing psychological and physical health problems, and the specific form in which those problems are manifested (reviewed in [20]). A key question concerns the causes of those differences, particularly the ways in which they are shaped by genes, physiology, and socialization. The focus of this paper – in line with the other papers in this special issue of *Frontiers of Neuroendocrinology* – concerns the extent to which human behavioral sex differences are influenced by sex hormones present during sensitive periods of development acting to organize the brain.

More than 50 years ago, Phoenix et al. [130] provided an experimental demonstration in female guinea pigs that early exposure to androgens masculinized sexual behavior. This revolutionary work opened a new era in understanding sexual differentiation of behavior and led to thousands of studies in many species showing unequivocally that sex hormones present early in development affect sexual differentiation of behavior as well as reproductive anatomy and function [166]. These hormones are said to have "organizational" effects because they produce permanent changes to brain structures and the behaviors they subserve. They are contrasted with "activational" effects, that is, hormones acting later in life to produce temporary alterations to the brain and behavior (through ongoing changes to neural circuitry) as the hormones circulate in the body throughout adolescence and adulthood. The main distinctions between organizational and activational effects concern timing and permanence, although these distinctions are not absolute [3].

Organizational effects have generally been considered to occur early in life when the brain is undergoing rapid change, but there has always been consideration of potential other sensitive periods of brain development when sex hormones again act to induce permanent changes [166]. Recent work in nonhuman animals has focused attention on other particular periods when there are substantial – and relatively abrupt – changes in levels of sex hormones, and that might serve as additional opportunities for hormones to sculpt brain structure: puberty and pregnancy (e.g., [91,149]). In this paper, we consider how human psychological sex differences are influenced by organizational hormones during prenatal development and again during puberty. We consider the foundations of the work, the methods used to study the question, the evidence that prenatal and pubertal hormones produce long-term behavioral changes, and directions for future research. In

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doing so, we organize our review into three major sections: a discussion of the rationale and methods for studying prenatal life and puberty as sensitive periods for human psychosexual differentiation, the evidence for hormonal influences on key gendered characteristics (organized by characteristic) and a brief consideration of the neural mechanisms underlying the effects, and a summary and synthesis of the current state of the field, with suggestions for future work.

2. Background: sensitive periods during prenatal and pubertal development

As noted above, the work of Phoenix and colleagues [130] had a profound effect on thinking and study of psychological sexual differentiation. It is now clear from thousands of studies in nonhuman animals that the levels of sex hormones present during early development produce long-lasting effects on a variety of behaviors that show sex differences, including sexual behavior but extending well beyond to include, for example, learning and memory, aggression, and play (discussed in other papers in this special issue and reviewed in [9,10,62,139,160,165]). This evidence comes from experimental manipulations of hormones (e.g., castration of males, androgen treatment to females) and from natural variations (e.g., gestating between animals of the opposite sex). As detailed below, there is increasing evidence that human behavior is also influenced by levels of hormones present during prenatal development, with particular importance for effects of androgens.

Work in the past few years has heightened interest in the possibility that the brain continues to be organized by sex hormones well beyond the prenatal and early neonatal periods. In particular, on the basis of work in rodents, Sisk and her colleagues (e.g., [145,149]) have suggested that the brain remains sensitive to the effects of sex hormones into adolescence, undergoing structural changes as a result of hormone exposure. Initially, they suggested two separate periods – early development and adolescence – during which the brain is sensitive to sex hormones [149]; this is shown in the top panel of Fig. 1. In a modification to their original ideas, based on their evidence from Syrian hamsters, they proposed a continuum of sensitivity, with sensitivity at its peak during early development, declining throughout the juvenile and adolescent periods, and ending sometime in late adolescence or early adulthood [145]; this is shown in the bottom panel of Fig. 1.

Evidence from several labs suggests that rodent behavior is indeed modified in permanent ways by sex hormones present during adolescence, with particular effects of variations in pubertal timing; the evidence is discussed by Sisk and colleagues [145,149]. We emphasize several aspects of these effects because they are relevant for sexual differentiation of human behavior. First, the later period of brain organization builds on and refines neural circuits that were initially established by sex hormones during early development. So, sexual differentiation begins early in development and is reinforced and finished later in development. This suggests that human sex-typed behavior depends on appropriate hormone exposure at multiple points in development. Second, most evidence concerns effects of androgens on male-typical behavior, especially sexual behavior, but there is some evidence for an active feminizing effect of ovarian hormones on female-typical behavior especially during puberty. The latter has particularly intriguing implications for human behavior: Effects of prenatal hormones have been found to relate exclusively to the masculinizing (and defeminizing) effects of high levels of androgens; it now seems possible (indeed likely) that feminization is an active process facilitated by ovarian hormones in adolescence. Third, a continuum of sensitivity means that variations in pubertal timing – and corresponding variations in availability of sex hormones at different points of sensitivity – have consequences for brain organization and subsequent behavior. This has implications for understanding key aspects of human adolescent psychological development, particularly the well-documented adverse behavioral outcomes of early puberty in girls. Fourth, social experiences may partially compensate for hormone deficiencies at puberty. This complicates attempts to understand how behavioral changes at puberty reflect brain changes directly created by hormones versus social experiences.

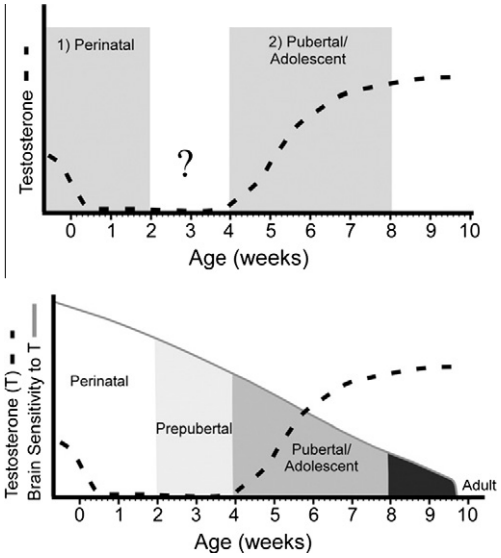

Fig. 1. Proposals from Sisk and colleagues about multiple sensitive periods for organizational effects of sex hormones, based on work in Syrian hamsters. Reprinted from [145] with permission from the author and publisher. Top. Two-stage model for steroid-dependent organization of behavior. Testosterone secretions during the perinatal and adolescent periods organize adult mating behavior. The dashed line approximates testosterone secretions across development, and the shading denotes the approximate timing of perinatal and adolescent development in the Syrian hamster. The question mark highlights that less is known about T-dependent behavioral organization in the time between the perinatal and adolescent periods. Bottom. Model of declining sensitivity for organization effects of testosterone. Illustration based on evidence of effects of early, on-time, and late adolescent testosterone treatments on adult mating behavior. The data suggest that adolescence is part of a protracted sensitive period for the organizing actions of testosterone (area under the solid gray curve), and that sensitivity to the organizing actions of testosterone decreases across postnatal development. The dashed line approximates testosterone secretions across development, whereas the solid line depicts decreasing sensitivity to the organizing actions of testosterone across development. Shading approximates the timing of perinatal, prepubertal, adolescent, and adult periods in the Syrian hamster.

3. Methods for studying behavioral effects of organizational hormones

Studying organizational effects on human behavior is challenging because it is not possible to manipulate hormones in people, and human pregnancies rarely consist of multiple fetuses. But much has been learned from natural experiments (individuals with endocrine disorders) and from examining natural variations in hormone exposure. These methods are summarized in Table 1, and described below.

3.1. Studying effects of prenatal hormones

Human behavioral effects of prenatal hormones have primarily been studied in individuals whose hormone levels were atypical for their sex during early development as a result of a disorder of sex development (DSD) or maternal ingestion of drugs during

Table 1
Methods for studying human behavioral effects of organizational hormones.

Condition	Karyotype	Effective prenatal hormones	External genitalia/usual rearing sex	Effective pubertal hormones	Test of prenatal hormone effects	Test of pubertal hormone effects
Congenital adrenal hyperplasia, classic	46,XX	↑ A	Ambiguous/Female	nl ♀ A & E w/Rx	Moderate A	
Complete androgen insensitivity	46,XY	no A	Female/Female	no A	Low A	
Partial androgen insensitivity	46,XY	↓ A	Ambiguous/Varies	↓ A	Low-moderate A	
Cloacal exstrophy	46,XY	nl ♂ A	Absent penis/Female	↓ A if ♀	High A	
5α-Reductase deficiency	46,XY	nl ♂ T levels, ↓ DHT	Ambiguous, Male puberty/Varies	↑ A	Moderate A (T vs. DHT)	High A
Idiopathic hypogonadotropic hypogonadism	46,XY	nl/↓ A	Male/Male	↓ A, nl A w/Rx	Low A?	Low A, Timing of A
Congenital adrenal hyperplasia, nonclassic	46,XX	nl ♀ A	Female/Female	↑ A, nl A w/Rx		High A, Timing of A
Polycystic ovary syndrome	46,XX	nl ♀ A	Female/Female	↑ A, nl A w/Rx		High A, Timing of A
Precocious puberty, girls	46,XX	nl ♀ E	Female/Female	↑ E early		Timing of E
Delayed puberty, boys	46,XY	nl ♂ A	Male/Male	↓ A early		Timing of A
Gender dysphoria with suppressed puberty, girls	46,XX	nl ♀ E	Female/Female	↓ E		Low E
Gender dysphoria with suppressed puberty, boys	46,XY	nl ♂ A	Male/Male	↓ A		Low A

Adapted and modified [169].
nl: Normal; A: androgen; E: estrogen; T: testosterone; DHT: dihydrotestosterone; ↑: increase; ↓: decrease; Rx: treatment.

pregnancy to prevent miscarriage. Increasingly, evidence from these unusual samples has been supplemented by data from normal individuals with typical variations in hormones.

3.1.1. Natural experiments

The most extensively studied natural experiment is congenital adrenal hyperplasia (CAH), a genetic disease that results in exposure to high levels of androgens beginning early in gestation because of an enzyme defect affecting cortisol production [68]. The condition is usually detected at birth, and androgen levels normalized with cortisol replacement. Both sexes are affected by CAH, and both have been studied behaviorally, but studies in nonhuman species suggest more effects of excess androgens in females than in males. Therefore, if human psychological sex differences are affected by androgens present during early development, then females with CAH should be more male-typed and less female-typed than a comparison group of females without CAH. Studies of females with CAH were begun shortly after the publication of the work of Phoenix et al. [130], because they were seen to be a good model for extending animal work to human beings (e.g., [117]).

CAH is not a perfect experiment for several reasons, most prominently masculinized genitalia resulting from high levels of prenatal androgen, abnormalities in hormones other than androgen, atypical postnatal hormones (due to imperfect disease control), and the consequences of living with a chronic illness (see discussion in [20]). Such alternative explanations have generally not been found to be important for behavior in females with CAH (see discussion below), but it is important to seek converging evidence for findings in CAH.

There are a variety of other conditions in which prenatal androgen exposure is separated from rearing sex, providing additional opportunities to examine how prenatal androgens affect behavior [68]. Most of these conditions are much rarer than CAH, so they have not been well studied. In cloacal exstrophy, boys with XY karyotype and male-typical prenatal androgen exposure have genital defects that frequently lead to castration at birth and rearing as a girl. In ablatio penis, boys with normal male development (XY and normal androgen exposure) have had an accidental removal of the penis that usually leads to castration and rearing as a girl. In both cloacal exstrophy and ablatio penis, androgen effects on behavior should cause these individuals to be more male-typed and less female-typed than a comparison group of females (although masculinized behavior could also reflect effects of genes on the Y chromosome). In micropenis or partial androgen insensitivity, individuals with a Y chromosome are exposed to lower levels of androgen than is typical for males, with some reared as girls and some reared as boys. If androgen affects behavior (regardless of rearing sex), they should be less male-typed than typical boys and more male-typed than typical girls. In complete androgen insensitivity, individuals with male-typical chromosomes and normal testes have defective androgen receptors and are thus unable to respond to the androgens that are produced by their testes, so they have female-typical physical development. If androgen affects behavior, they should be similar to typical females (although feminized behavior could also reflect effects of female-typical rearing). In 5α-reductase deficiency (5α-RD), individuals with XY karyotype and normal testes cannot convert testosterone into dihydrotestosterone, so their external genitalia are not fully masculinized at birth and most of them are reared as girls. But, they virilize at puberty, developing a penis and other physical features usually affected by testosterone at puberty, such as a beard and male physique. They provide a particularly interesting test of the relative effects of androgens during prenatal development versus at puberty.

3.1.2. Typical variations

Natural experiments all have limitations, so it is important to study whether prenatal androgens affect behavior among typical individuals. Although it is not easy to measure hormones during prenatal development, several researchers have successfully examined hormones in amniotic fluid and then related these hormones to later behavior; this method was first proposed and used by Finegan and colleagues [52].

Because such studies are difficult to conduct, there has been considerable interest in studying indirect indicators of presumed prenatal testosterone exposure to relate to contemporary behavior in children and adults. These indicators include sharing the uterine environment with an opposite-sex fetus (co-twin), and markers such as fingerprint patterns, relative ratio of the second to fourth finger (2D:4D ratio), and otoacoustic emissions (sounds produced by the ear). Only one of these indicators – digit ratio – has been convincingly shown to relate to prenatal androgen exposure, but the link is modest, and therefore digit ratio is not a good indicator of individual differences in androgen exposure [15]. Therefore, we

will only consider links between psychological characteristics and these markers in select cases.

3.2. Studying effects of pubertal hormones

There is some work investigating behavioral effects of pubertal hormones, but they have not been explicitly designed to examine puberty as an organizational period. Instead, they have focused on pubertal hormones as activators of neural circuits established earlier, as triggers of genetic vulnerabilities, or as indicators of physical maturity that serve as social cues (discussed in [57,157]). Nevertheless, as discussed in the following section, some of that work can be interpreted as tests of organizational effects of pubertal hormones.

In discussing methods for examining puberty as another organizational period (using natural experiments and variations in typical samples), we consider how to test both possibilities suggested by Sisk and her colleagues – whether puberty is a second organizational period, separate from (but refining) the first prenatal period [149], or whether it represents a time of continuing, but declining sensitivity to hormones [145]. We also consider whether the hormones that likely serve to organize the brain at puberty differ from those that do so early in development. Evidence regarding prenatal hormone effects in human and nonhuman primates makes clear that androgens are the masculinizing agent (e.g., [33,166]); estrogens probably do not have any effect because both sexes are exposed to estrogens from the mother [68]. But, at puberty, there are dramatic sex differences in both androgens and estrogens, and it is reasonable to hypothesize that both types of hormones act on the brain at that time.

3.2.1. Puberty as a time of declining hormone sensitivity

This idea is relatively easy to test: individuals who mature early should be more affected by sex hormones than those who mature late, because they are exposed to hormones when the brain is relatively more sensitive. There are a number of opportunities to test whether sensitivity to sex hormones declines across development; long-term behavioral outcomes should vary with timing of puberty and thus timing of exposure to high levels of sex hormones.

The most direct way to examine declining hormone sensitivity with age is to take advantage of typical variations in pubertal development [159]. Those who mature early should differ behaviorally from those who mature later – and these differences should persist well beyond puberty. Differences should be most apparent on characteristics that show the largest sex differences, with early maturers more sex-typed than late maturers.

The limitation of this design – comparing early and late maturers – concerns the confound between physical maturity and social experiences: youth who mature early are likely to be treated differently (and perhaps in a more sex-typed way) than those who mature later [157]. In fact, a prominent hypothesis regarding gender development at adolescence focuses on "gender intensification" [79], the notion that the developmental trajectories of girls and boys increasingly diverge in adolescence as a result of the convergence of biological, social, and cognitive changes. In this view, the physical changes of puberty are seen to mark the onset of sexual maturity and direct attention to looming adult roles; this leads to changes in adolescents' self perceptions and in reactions from socialization agents in ways that accentuate gender-typed activities, interests, and self perceptions [79].

Further complicating psychological studies of variations in pubertal timing is the way that timing is typically measured [47]. Many investigators use age at menarche which can be reported with considerable accuracy. But menarche is relatively late in puberty, so it is not a good indicator of the timing of gonadal hormone increase. Another common measure involves child or parent reports of the child's developmental status on a variety of physical indicators, such as growth spurt, body hair, and genitalia (breasts in girls, penis in boys), leading to a summary score of pubertal development. Concerns about the measure include only moderate validity, and failure to separate the different components of puberty (and thus perhaps failure to capture hormone changes characterizing the sensitive period).

An opportunity to overcome the limitations involved in studying typical children comes from children who have abnormal pubertal timing or absent puberty. Pathologically early or late puberty generally results in clinical diagnosis and hormonal treatment [156]. Precocious puberty is more common in girls than in boys, whereas delayed puberty is more common in boys than in girls. Precocious puberty often occurs as early as 5 years of age, and children this young are unlikely to be viewed as mature, so studies of precocious puberty do not have the limitations of studies of early normal puberty. Children with precocious puberty are generally treated with gonadotrophin-releasing hormone agonists (GnRHa) to suppress puberty, until they reach the age at which puberty typically occurs [27]. Girls with precocious puberty provide an opportunity to study several questions about puberty as another sensitive period: whether organization depends on the presence of sex-typical hormones (versus androgens in both sexes) and whether sensitivity is greatest if hormones are present early. If estrogens are important and sensitivity declines across age, then girls with precocious puberty should be extremely sex-typed. Further, degree of sex-typing should be related to timing of treatment, with later GnRHa (more early exposure to estrogens) treatment associated with more sex-typing.

Children with delayed puberty are treated with sex-typical hormones (testosterone in boys, estradiol in girls). Behavioral effects of delayed puberty depend on which hormones are important for brain development. If exposure to sex-typical hormones is important (androgens in boys, estrogens in girls) then delayed puberty should be associated with less sex-typing in both boys and girls compared to those with normal pubertal timing. Further, degree of sex-typing should be related to timing of treatment, with early sex hormone treatment associated with more sex-typing.

Puberty may also be completely absent. In some cases, this results from known disorders of development, for example, androgen insensitivity syndrome or sex chromosome anomalies such as Turner Syndrome. In such cases, sex-typical hormones are used to induce development of secondary sex characteristics (although they cannot induce reproductive function) and to maintain bone health. These youth provide another opportunity to determine the role of pubertal hormones in organizing sex-typed behavior: timing of hormone treatment should be associated with degree of sex-typing. In those few cases where treatment was not implemented (especially in the past when treatment was not available), individuals should be sex-atypical in their behavior if pubertal hormones are essential to complete the development of psychosexual function.

It is important to note, however, that these methods are not perfect for testing whether puberty is a second organizational period. First, individuals who have disordered puberty (especially delayed or absent puberty) often have conditions that also lead to low levels of prenatal hormones. Second, treatment for delayed or absent puberty often occurs quite late, perhaps past the maximal period for hormone sensitivity. Third, most studies of individuals with disordered puberty only include assessment during treatment, and do not involve follow-up beyond puberty, so it is difficult to differentiate effects of activational hormones from organizational ones.

3.2.2. Puberty as a trigger for normative changes

Puberty may serve as a separate discrete sensitive period, acting to trigger changes in all adolescents. On the one hand, it seems simpler to study behavioral effects of pubertal hormones than of prenatal hormones, because pubertal hormones can be more easily

measured than prenatal ones. On the other hand, there is a key difference between prenatal and pubertal hormones that makes it difficult to examine the long-term effects of the latter: sex hormones increase at puberty and remain high through much of adult development, whereas prenatal testosterone peaks during weeks 8–24 of gestation and then declines and, except for a brief neonatal surge, stays low throughout childhood [150]. Thus, links between pubertal sex hormones and concurrent adolescent behavior could reflect either organizational or activational effects; similarly, longitudinal links between pubertal sex hormones and later adult behavior could reflect organizational effects or activational effects if individual differences in hormone levels are stable.

An opportunity to examine the long-term impact of hormones at puberty might be provided by individuals who have endocrine disorders that manifest at puberty and who receive treatment to control their hormones. This includes polycystic ovary syndrome (PCOS) and nonclassical CAH (NC-CAH). PCOS is associated with excess androgens in girls and women, and may be treated with medications to reduce androgen levels [6]. NC-CAH is associated with mild to moderate cortisol deficiency, and thus with mild to moderate androgen excess beginning at varying times during postnatal development; it may be treated with cortisol replacement to reduce androgen levels [152]. A test of the long-term effects of pubertal hormones would require studies of subgroups whose androgen excess begins precisely at puberty and whose treatment begins at a later time; they could also provide a test of the importance of timing of androgen excess by comparing individuals with early versus late disease onset. This is not an easy task, because PCOS is often not diagnosed until later in adolescence or early adulthood, and NC-CAH has onset at varying times from infancy into adulthood. Thus, the current psychological studies of women with PCOS or NC-CAH will not be reviewed because they do not consider timing of disease onset and treatment. Further, these conditions may not provide a perfect test of puberty as a second organizational period if that period "finishes" what was started prenatally because their prenatal exposure is not obviously atypical.

Another opportunity to examine whether puberty is an organizational period is provided by children with gender identity disorder who receive GnRHa treatment to suppress puberty (in order to provide time to decide about gender reassignment) [41,76,176]. It will be interesting to compare – in a randomized clinical trial – those who had a sex-typical puberty with those whose puberty was suppressed in terms of sex-typed characteristics (including gender identity but also cognitive abilities and personality traits). If pubertal testosterone organizes the male brain, then gender dysphoric boys who receive GnRHa should be less male-typed (e.g., have lower spatial ability and aggression, be more likely to seek sex-reassignment) than those who have a typical puberty. Similarly, if pubertal estradiol organizes the female brain, then gender dysphoric girls who receive GnRHa should be less female-typed (e.g., have higher spatial ability and less interest in babies, and be more likely to seek sex-reassignment) than those who have a typical puberty. As with other natural experiments assessing effects of pubertal hormones, it is important to examine behavior beyond puberty (to ensure that effects are not activational), and a limitation concerns the extent to which effects of pubertal hormones depend on prenatal ones. Systematic studies of GnRHa treatment in youth with gender identity disorder are just emerging, and the focus so far has been on mental health outcomes during treatment, not on gendered characteristics (beyond gender dysphoria) after adolescence.

3.3. Summary: methods for studying behavioral effects of organizational hormones

As discussed above, there are a number of good options for studying whether sex hormones produce permanent changes to behavior in human beings, as they do in other species. Methods for studying effects of prenatal hormones are better established and more widely-used than those for studying pubertal hormones, but there are a number of opportunities for the latter. It is easier to study puberty as a time of declining sensitivity (assessed by examining variations in pubertal timing) than of puberty as a second organizational period, and therefore the work discussed below provides more evidence on the former than the latter. It is important to remember, however, that these natural experiments vary in their ability to determine whether puberty "finishes" effects started during the prenatal period.

4. Behaviors likely to be organized by sex hormones during prenatal and pubertal development

Studies in nonhuman animals make clear that sex hormones influence behaviors that show sex differences. Thus, hormones should influence human characteristics that show sex differences. Further, organizational effects at puberty might be expected to result in behavioral changes in adolescence, so it is important to consider characteristics that are known to change in adolescence.

4.1. Psychological sex differences

There are many psychological characteristics that show such differences, with some differences larger than others. Some have suggested that sex differences are relatively scarce and small [83] and there are many ways in which the sexes are psychologically similar, but sex differences are among the largest and robust effects in psychology (see comparative data, e.g., in [116]). Although there are numerous domains that show sex differences (reviewed in [20,138]), we focus in this paper on characteristics that have been discussed in relation to hormones during prenatal or postnatal development. As discussed in later sections, this includes gender identity, sexual orientation, sex-typed activity interests, sex-typed cognitive abilities, and sex-related behavior problems and forms of psychopathology. There are also sex differences in many personality traits and social behaviors, such as aggression, risk-taking, infant-directed behavior, and emotion recognition, but there is not much evidence regarding hormonal influences on these characteristics, so we do not include them in this review except as they are related to the other characteristics we discuss (e.g., aggression in relation to behavior problems).

Prenatal hormones can organize the brain to subserve behavior at any point in development, whereas pubertal hormones would affect behaviors beginning in adolescence. So, an important consideration in looking for organizational effects at different developmental periods concerns developmental changes in sex differences. If puberty is another organizational period, then there should be change in the nature and/or magnitude of sex differences at the pubertal transition. In particular, sex differences should emerge or increase at puberty as a result of actions of organizing hormones. The specific nature of changing sex differences depends on two related questions about hormones: (a) whether estrogens have a role in feminizing behavior at puberty; (b) whether the relevant pubertal hormones are sex-differential (androgens for boys, estrogens for girls) or whether androgens are responsible for sexual differentiation in puberty as they are in the prenatal period (with boys having high levels and girls having low levels).

4.2. Psychological changes in adolescence

We consider two types of psychological changes in adolescence. First, there are changes that are normative. Most individuals experience those changes, but to varying degrees. For some youth, those

changes become pathological, perhaps because of genetic vulnerability or environmental disadvantage. We consider the extent to which such changes are influenced by normative changes in hormones at puberty, with the additional possibility that variations in levels of those hormones could account for variability in degree of change. This type of change represents puberty as an independent organizational period (Fig. 1, top panel). Second, there are changes that vary as a function of the timing of the individual's hormone exposure. Some individuals experience those changes, but many do not. This type of change represents puberty as a period of declining hormone sensitivity (Fig. 1, bottom panel).

4.2.1. Normative changes in adolescence

As noted above, a prominent hypothesis about gender development in adolescence concerns gender intensification. In support of their hypothesis, Hill and Lynch [79] documented sex differences in a variety of domains that appeared or increased during the second decade of life, including internalizing symptoms (greater anxiety and self-esteem problems in girls than in boys), achievement (favoring boys), and social relationships and social behavior (with girls more than boys oriented to relationship intimacy and boys more than girls inclined to exhibit physical aggression). They noted, however, that there was a lack of longitudinal data needed to document the hypothesized patterns of *change* from childhood to adolescence or the sources of those changes. Unfortunately, almost 30 years later we have only a little data speaking to changing patterns of sex-typed characteristics in adolescence; these data are discussed below where they are relevant.

Perhaps the most salient change is the increased risk-taking that occurs in early adolescence; this can lead to delinquency, substance use, risky sex, and problem behaviors. Detailed discussion of the nature and proposed explanations for these changes will be discussed in Section 9 when we consider hormonal influences on behavioral problems.

Another major – but underappreciated change – in adolescence concerns face processing, when the processing characteristic of childhood is replaced by adult-like face processing. Children process faces in a piecemeal fashion, whereas adults process faces in a holistic fashion [29]. For example, upright and upside-down faces are remembered in similar ways by children, but adults show superiority for upright over upside-down faces. Processing shows a transition in early adolescence, when children begin to show the same effects as adults, that is, remembering upright faces much better than upside-down ones [28]. These behavioral differences are paralleled by brain activation differences, with different developmental trajectories for brain activation of faces versus objects and places. Children were seen to have adult-like organization in cortical regions subserving object- and place-recognition, but adult-like patterns of activation for faces did not emerge until adolescence [143].

It is likely that these changes in face processing in adolescence are influenced by sex hormones and have implications for the other psychological changes that take place at that time. The likelihood of hormone effects is increased in light of sex differences in face processing: Females are better than males in face detection; the sex difference is reduced for detection of upside-down faces and is not present for objects (e.g., trees) [106]. Unfortunately, there is no evidence on pubertal hormone effects on face processing, so it is not considered further in this paper. But this domain represents a fruitful one for investigating puberty as an organizational period with consequences for sex-linked psychopathology.

4.2.2. Psychological correlates of variations in pubertal timing

Puberty also has varying psychological significance as a function of the age at which it occurs. There are differences among youth who mature early versus on time versus late, with most of those differences apparent during adolescence, and little evidence about their permanence. Because these psychological differences are specific to a few types of behavior, we discuss them in later sections as appropriate.

5. Sex-typed activity interests: evidence for organizational hormonal effects

5.1. Sex differences in activity interests

One of the largest and most important sex differences concerns interests [20,138]. In childhood, boys and girls prefer and engage with different toys and participate in different activities (e.g., dance, sports). In adolescence, boys and girls continue to prefer and participate in different leisure and household activities, and academic pursuits. In adulthood, men and women continue to prefer and participate in different activities, and are differentially represented in different occupations. Although the sexes overlap in their interests and activity participation, the average differences are large to very large. Interests are important because they are reasonably stable, and shape future career choices, especially with respect to domains such as mathematics and the physical sciences [45].

Interest and participation in gendered activities are often considered to result from socialization, and there is indeed evidence showing effects of social agents, including parents' expectations (e.g., [49,122,148]), parents' attitudes and modeling of gender roles [161], siblings' modeling of attitudes and involvement in sex-typed leisure activities (e.g., [109]), and peer interactions [103]. But, there is also good evidence that gendered interests and activities are influenced by hormones, at least during prenatal development.

5.2. Prenatal hormone effects on sex-typed activity interests

5.2.1. Evidence from CAH

Data from several groups and countries, with a variety of sound methods (including observations, self-reports, and parent-reports) make clear that girls and women with CAH are sex-atypical in their activity interests, showing more male-typed and less female-typed interests than do girls and women without CAH (in most studies, their unaffected sisters). Thus, for example, compared to their unaffected sisters or unrelated controls, girls with CAH play more with boys' toys and less with girls' toys, and report themselves and are reported by their parents to be more interested in male-typed toys and activities and less interested in female-typed toys and activities [17,112,126,127]; when given a toy to keep, they are more likely to pick a boys' toy (such as a toy airplane) [19]; girls with CAH make drawings that are more like those of typical boys than typical girls, using masculine characteristics (such as moving objects, dark colors, a bird's-eye perspective) more than feminine characteristics (such as human figures, flowers, light colors) [85]. Females with CAH continue to be interested in male-typed activities into adolescence and adulthood, although the evidence here is based on self-reports and not on observations. Thus, compared to their sisters, teenage girls with CAH report greater interest in activities like electronics, cars, and sports, and less interest in activities like cheerleading, make-up, and fashion [12]. Adult women with CAH report that they are more interested than are their sisters in male-typed activities, such as sports and electronics [113]. Across age (childhood, adolescence, and adulthood), females with CAH also express interest in male-typed careers, such as engineer, construction worker, and airline pilot [12,113,126]. These interests manifest themselves in behavior: adult females with CAH engage more in male-typed occupations than do females without CAH [56]. Differences in interest between females with and without CAH are very large, with little overlap between the groups. It is

characteristic of girls and women with CAH to be interested in male-typed activities.

But, CAH is not a perfect experiment, so it is important to ensure that their male-typed interests specifically reflect prenatal exposure to high levels of androgens and not social responses to masculinized genitalia or factors related to the disease itself. Several pieces of evidence strongly implicate androgens in the masculinized interests of females with CAH. Observational data suggest that parents do not encourage male-typed play in their daughters with CAH, and may actually encourage female-typed play [126,127]. Further, sex-typed interests in females with CAH have been linked directly to their degree of prenatal androgen exposure measured by genetic mutation and disease severity [16,113,126]. Thus, there is a dose–response relation between prenatal androgen exposure and sex-typed activity and occupational interests.

5.2.2. Evidence from other clinical conditions

Converging data for androgen effects on activity interests come from other clinical conditions. These include children with a Y-chromosome who were reared as girls due to cloacal exstrophy, ablatio penis, or ambiguous genitalia due to lower-than-typical male prenatal androgen levels. Reports from two cases of ablatio penis and a small series of boys with cloacal exstrophy who were reared as girls indicate that they are interested in male-typed activities and occupations [24,35,44,133].

In a systematic assessment of children with XY karyotype but low (for boys) prenatal androgen exposure, sex-typed play was found to be directly related to degree of prenatal androgen exposure [89]. Further, time spent playing with boys' toys did not depend on whether the children with intermediate androgen exposure were reared as boys or as girls.

5.2.3. Evidence from typical samples

Findings from females with CAH have been confirmed in children who show normal variation in prenatal hormone levels measured from amniotic fluid. Of particular note is a study showing links in both boys and girls between amniotic testosterone levels and male-typed play at ages 6–10 [5]: the most male-typed interests and characteristics (as reported by parents on a widely-used measure) were found in children who had high levels (for their sex) of naturally-occurring prenatal testosterone.

5.2.4. Inconsistent data

Some studies do not confirm the findings described above, and there are a number of reasons for failures to find effects. Two studies of twins failed to find differences in sex-typed toy play between children with same- versus opposite-sex co-twins [77,137]. But, it is not clear if testosterone is transferred to the female twin in high enough levels at the right time in development to masculinize activity interests. Two studies examining amniotic hormones failed to find a relation between testosterone and play activities. The first involved 13-month old infants, and sex differences are smaller at this age than at later ages [162]. The second involved 4- to 6-year-old children [95] and the failure to detect a link between fetal testosterone and play might reflect factors such as limited variability in testosterone or insufficient statistical power. It is unclear how this sample overlaps with the one reporting associations at a later age [5]. Studies of amniotic hormones also suffer from having only a single sample of hormones that may not have been obtained during the sensitive period for the development of brain regions involved in play preferences.

5.3. Pubertal hormone effects on sex-typed activity interests

There is no specific evidence regarding effects of pubertal hormones on sex-typed interests. Indirect evidence suggests that there are not independent effects because sex differences in activity interests do not appear to increase in adolescence, and interests appear to be stable across time. But, these conclusions are based more on cross-sectional than on longitudinal data, and there are no direct data, so it is not possible to rule out effects on sex-typed interests of pubertal hormones.

5.4. Summary: Organizational effects on sex-typed activity interests

Evidence from a variety of sources converges to indicate that sex-typed activity interests are strongly influenced by prenatal androgens. This organizational effect is seen across a wide age range, from the toddler years into adulthood. Because the current evidence is more compelling from DSDs than from typical samples, there is more confidence in concluding that androgen affects differences between the sexes than variations within each sex. There is no evidence that hormones at puberty have an effect on sex-typed activity interests, but this issue has not been systematically studied.

6. Gender identity: evidence for organizational hormonal effects

6.1. Demographics of gender identity

The largest psychological sex difference is in gender identity: the overwhelming majority of girls and women are female-identified, and the overwhelming majority of boys and men are male-identified. But some people identify as a member of the other sex, and this is known as gender identity disorder; a subclinical form is called gender dysphoria. There are no epidemiological data on the prevalence of gender identity disorder. About 2–5% of children are estimated to have gender identity disorder or subclinical variants [174]. Boys are referred for treatment more than girls, three to six times more in childhood, but only 1.2–1.3 times more in adolescence [172]. This may reflect referral bias due to cultural factors; for example, beliefs that girls may outgrow cross-gender behavior, and less tolerance of cross-gender behavior in boys than in girls. Girls display more extreme cross-gender behavior than boys before a clinical assessment is obtained [174]. In adults, prevalence estimates range from 1 in 11,000 to 1 in 37,000 for men, and 1 in 30,000 to 1 in 150,000 for women [174]. Although there are no data showing change in prevalence of gender identity disorder across development, the prevalence estimates and follow up of children with gender identity disorder (as discussed below in Section 6.3) suggest that it declines with age.

6.2. Prenatal hormone effects on gender identity

In contrast to the strong effects of androgen on activity interests, androgen does not appear to have a large effect on gender identity, especially when androgen is only moderately elevated (as happens in most natural experiments).

6.2.1. Evidence from CAH

The evidence from females with CAH is very consistent in several ways [14,43,80,112,115,175]. The overwhelming majority identify as female throughout life. The very small number (<5%) who are unhappy as females or live as males are *not* necessarily those who have the most masculinized genitals or had the most prenatal androgen excess. Interestingly, the amount of gender dysphoria is about the same in the few who are reared as boys [43].

6.2.2. Evidence from other clinical conditions

Other evidence comes from conditions that are very rare, with small samples and variable assessment of gender identity. Never-

theless, the evidence does converge with that from females with CAH to suggest that gender identity is variable in individuals with sex-atypical prenatal androgen exposure (such as micropenis), and that this variation in gender identity is not strongly related to prenatal androgen exposure [89,105,171]. In general, gender identity is more predictable from rearing than from prenatal androgen exposure, but rearing sex itself is probably not random (e.g., boys with more masculinized genitalia are more likely to be reared as boys than those with less masculinized genitalia). Evidence from XY individuals with high sex-typical androgen levels reared as girls because of genital defects or accidents to the penis also show variability in gender identity, with some identifying as male and some as female (e.g., [24,35,44,133,144]). Even in those children who did reassign themselves to male, it is not clear that androgen alone is responsible for the gender change; the social environment of these children is probably complicated. A review of the world's literature shows that most XY individuals with abnormal or absent penis (including, but not limited to ablatio penis and cloacal exstrophy) who are reared as girls grow up to identify as girls and women, and to be happy with their assigned sex [111].

Further evidence against androgen as an exclusive determinant of gender identity is provided by individuals with gender dysphoria or transsexual identity who have normal genitalia and no obvious signs of abnormal prenatal hormone exposure (e.g., [173]). It is, of course, possible that some aspects of psychological sexual differentiation occur later than physical sexual differentiation, and that different aspects of behavior are influenced by prenatal androgens during different prenatal periods, as has been seen in monkeys [61]. But, some of the most compelling behavioral differences between gender dysphoric and typical children are seen in their childhood play interests [174], which appear to be influenced by androgens during early development, as shown, for example, in the high correlation between toy interests and genital virilization in girls with CAH [16].

Some have argued that gender identity is largely – if not exclusively – determined by prenatal androgens. Evidence cited to support this position comes from a few remarkable cases of male gender identity in XY individuals with male-typical prenatal androgen exposure reared as girls (e.g., [44,133,140]). But, the systematic evidence noted above paints a complex picture, as articulated in a review of gender identity outcome in XY individuals reared as girls: "The findings clearly indicate an increased risk of later patient-initiated gender reassignment to male after female assignment in infancy or early childhood, but are nevertheless incompatible with the notion of a full determination of core gender identity by prenatal androgens" ([111], p. 423). Other evidence claimed to support a biological basis for gender identity are brain differences associated with transsexualism (e.g., [140]). But, experience changes the brain, so it is unclear whether the brain differences cause or result from atypical identity.

Thus, the evidence clearly shows that gender identity is associated with prenatal androgen exposure to a lesser extent than other gendered characteristics as discussed in this paper. Moderate levels of androgen present during prenatal development do increase the likelihood of male gender identity but they in no way guarantee it, and sex-atypical gender identity may occur in the absence of any indication of atypical hormone exposure. The other biological and social factors that modify androgen effects on gender identity are as yet unknown.

6.3. Pubertal hormone effects on gender identity

There are some intriguing data suggesting that gender identity might be influenced by hormones at puberty. In particular, evidence from natural experiments suggests that normal sex-typical hormone exposure at puberty influences gender identity in a direction that is consistent with those hormones (androgens leading to male identity, estrogens leading to female identity).

6.3.1. Declining sensitivity: effects of timing

There is no information on links between pubertal timing and gender identity. It would be interesting to study this question in typical individuals, because it is reasonable to hypothesize that early maturers would develop a stronger gender identity than late maturers.

6.3.2. Trigger for normative change

Some of the most interesting data about androgen effects on gender identity came from individuals with XY karyotype and 5α-reductase deficiency (5α-RD). An early study of gender identity in 5α-RD showed that most individuals changed gender from female to male at puberty; this was interpreted to reflect the prominence of hormones over social rearing in the determination of gender identity [86]. Although the data strongly suggest a role for pubertal hormones in gender identity, interpretation is confounded by several factors: gender identity change accompanied bodily change; the condition was known in the community, so the individuals might have been recognized and reared with the expectation that they would eventually become male; males had more freedom and status in the community than did females, perhaps increasing motivation to identify with the valued sex.

A review of the world's literature on individuals with 5α-RD [34] confirms that the majority (about 60%) of those reared as girls changed gender at puberty. The ones who changed gender were not necessarily those with the most masculinized genitalia, consistent with the data from girls with CAH, and consistent with androgen acting at puberty rather than during prenatal development.

Data confirming the importance of pubertal hormones in gender identity comes from outcome studies of children with gender identity disorder, showing that the majority develop gender *typical* identity in adolescence and adulthood, although many continue to display sex-atypical characteristics. An early study of extremely feminine boys showed that most developed a homosexual orientation without gender dysphoria [64]. Two recent studies confirm that most children with gender dysphoria do not remain dysphoric after puberty. In one follow-up study of girls with gender identity disorder in childhood, only 12% were found to have gender dysphoria in adulthood; most developed a heterosexual orientation without gender dysphoria, although there were elevated rates of nonheterosexual orientation [48]. In another study of boys and girls with gender dysphoria in childhood, 27% of boys and 64% of girls were still gender dysphoric, and most had nonheterosexual orientation [167]. Both studies showed evidence of a "dosage" effect: children with more childhood cross-sex behavior or gender dysphoria were more likely to be gender dysphoric at follow up. (This may explain why girls were more likely than boys in the second study to persist in dysphoria; they probably had to be more extreme to receive a diagnosis in the first place.) Additional evidence for the importance of puberty in gender identity comes from data showing reduced plasticity with age: individuals diagnosed with gender identity disorder in adolescence are more likely than those diagnosed in childhood to have persistent dysphoria into adulthood [172].

Nevertheless, testosterone at puberty is not essential for male gender identity. There are cases of male gender identity in individuals with male-typical chromosomes and prenatal androgen exposure who were castrated in early life and reared as girls because of genital defects (such as cloacal exstrophy or penile ablation [44,111,133]). Some typical girls develop gender dysphoria or male identity at puberty without any obvious exposure to testosterone [174].

6.4. Summary: organizational effects on gender identity

Evidence from a variety of DSDs converges to indicate that gender identity is only modestly affected by prenatal androgens. There is some suggestive evidence from individuals with DSD (especially 5α-RD) and from individuals with gender identity disorder that gender identity is influenced by exposure to sex-typical hormones at puberty (androgens in boys, estrogens in girls).

7. Sexual orientation: evidence for organizational hormonal effects

7.1. Demographics of sexual orientation

Another large sex difference is found in the target of sexual arousal: the overwhelming majority of men are aroused by women and the overwhelming majority of women are aroused by men. Estimates of nonheterosexual orientation vary by definition (e.g., experience, arousal, identity), method of assessment, age, sex, and culture. In general, nonheterosexual identity is estimated to occur in about 3–6% of men and 1–4% of women [141]. Although sexual orientation is generally not measured until mid-adolescence, there are correlated characteristics that develop earlier; for example, gay and lesbian adults are likely to show sex-atypical behavior in childhood [7].

7.2. Prenatal hormone effects on sexual orientation

Prenatal androgen affects the target of sexual arousal, with exposure to androgens increasing arousal to women. As is true for most other psychological characteristics, most evidence about hormonal influences on sexual orientation comes from women with CAH. Studies of sexual orientation are challenging because questions are very personal, and there are social constraints on both reporting and expressing homosexual behavior. Therefore, it is essential that such studies examine sample representativeness, use appropriate comparison groups, and measure arousal and not just experiences; the operationalization of sexual orientation deserves particular attention when interpreting and conducting this research [141].

7.2.1. Evidence from CAH

Several methodologically rigorous studies of sexual orientation converge to show increased nonheterosexual orientation in women with CAH. In general, the studies show that women with CAH have less heterosexual experiences but not necessarily more homosexual experiences than their sisters. But, in interpreting this result, it is important to consider constraints on same-sex behavior and the potential effects for women of having genitals that look different and that function differently (either from the disease itself or from the genitoplasty that is usually performed). Therefore, it is important to note that several studies show that, compared to their sisters or other typical women, women with CAH have more sexual interest (arousal and fantasy) in women and less sexual interest in men. For example, of 30 women with CAH, 20 reported exclusively heterosexual fantasies, 8 reported bisexual fantasies, and 2 reported no sexual fantasies; all 15 control women reported exclusively heterosexual fantasies [175]. Other studies indicate that about 15–25% of women with CAH are not exclusively heterosexual, with nonheterosexuality associated with higher prenatal androgen levels inferred from genotype [56,114]. One study showed no link between sexual orientation and outcome of genital surgery [125], further suggesting that sexual attraction to women results from exposure to high levels of prenatal androgens and not anatomical concerns.

The size of the difference in sexual orientation between women with and without CAH is moderate, reflecting the fact that most women with CAH are heterosexual in experiences and arousal. This contrasts with the fact that most girls and women with CAH have male-typical activity interests. It is possible, however, that the data on sexual orientation are less reliable than data on other characteristics, because of age effects on sexual orientation (nonheterosexuality increases in women in adulthood), unwillingness to answer honestly, or sample selectivity.

7.2.2. Evidence from other clinical conditions

There is some converging evidence for androgen effects on sexual orientation from other clinical conditions, although most data come from case reports. For example, two individuals with ablatio penis reared as girls reported sexual interest in women, despite the fact that one had male gender identity and the other female identity [24,35]. There is some suggestion from unsystematic reports that individuals with cloacal exstrophy reared as girls also report sexual attraction to women [111].

7.2.3. Evidence from typical samples

There is no direct evidence from typical samples regarding links between prenatal hormones and sexual orientation. It is difficult to obtain that information, even from maturing individuals enrolled in studies of amniotic hormones, given the low rates of nonheterosexual orientation. Therefore, we note (with appropriate caveats) that sexual orientation has been found to be related to two biomarkers, although the evidence is not entirely consistent. For example, lesbians, but not gay males, have been found to be masculinized in otoacoustic emissions [108], and in the relative length of the second to fourth fingers (2D:4D ratio) [66]. Further, gay men and lesbians are also more likely than same-sex heterosexual people to show sex-atypical interests measured directly in adulthood and retrospectively in childhood [7].

7.3. Pubertal hormone effects on sexual orientation

7.3.1. Declining sensitivity: effects of timing

If pubertal timing affects sexual orientation, it appears to do so in boys but not in girls. For example, data from a national probability sample in the US showed that gay and bisexual men reported an earlier age of puberty than heterosexual men, but lesbian/bisexual women did not report a different age of puberty than heterosexual women [23]. These results are consistent with those from nonrepresentative samples (discussed in [23]), but not consistent with data from another national sample [142]. An important question concerns causality in the link between pubertal timing and sexual orientation. In light of other prepuberty differences between gay and straight men, it seems most likely that the early puberty timing and sexual orientation reflect a common cause (e.g., degree of prenatal androgen exposure) rather than a causal link between pubertal hormones and sexual orientation.

7.3.2. Trigger for normative change

There is little information on the ways in which recognition or expression of sexual orientation is related to change in pubertal hormones. Adrenarche may be an important trigger to sexual attractions (both heterosexual and homosexual): Retrospective reports indicate that sexual attractions are noticed at about age 10 in both sexes; this was suggested to result from the rise in adrenal hormones characteristic of adrenarche [107]. It is unclear whether variations in levels of gonadal or adrenal hormones are associated with variations in sexual orientation, which become discernible at or shortly after puberty [141], but this is an opportunity for research.

7.4. Summary: organizational effects on sexual orientation

Evidence from several types of DSD indicates that sexual orientation is influenced by prenatal hormones, with exposure to moderately high levels of androgens increasing arousal to women. But, androgen influences are moderated by unknown factors, as shown, for example, by the variability in sexual orientation in women with CAH with apparently comparable prenatal androgen exposure. There has been little study of effects on sexual orientation of changing hormones at puberty, but the limited data suggest few effects.

8. Sex-typed cognitive abilities: evidence for organizational hormonal effects

8.1. Sex differences in cognition

The sexes do not differ in overall intellectual ability, but they do differ in the pattern of cognitive abilities [20,69]. The most reliable evidence about cognitive gender differences comes from adolescents and adults because of the difficulty in measuring these skills in children. For all abilities that show gender differences, the size of the difference varies by component ability and often by age.

The largest cognitive sex difference is in spatial ability, with males outperforming females in most aspects [69,99]; sex differences are most pronounced in mental rotation, and are moderate to large on tasks involving rotation of three dimensional objects [20,69]. There are also moderate to large differences in spatial perception, which requires recognition of the vertical or horizontal, targeting (i.e., hitting a target with a ball [90]), and abilities related to navigating in the real world [20,69]. There is one spatial domain in which females outperform males: memory for spatial location, and the difference is large [20,90].

The sex difference on verbal tasks is in the opposite direction. Females have a small to moderate advantage over males in a variety of verbal skills, including overall and general verbal skills, vocabulary, reading comprehension, essay writing, speech production, phonological processing, verbal fluency, and verbal learning and memory [20,69,74,84]. Females also outperform males on perceptual speed, with small to moderate differences [69].

8.2. Prenatal hormone effects on cognition

Evidence from multiple sources provides moderate support for the notion that prenatal androgens influence later spatial ability. Nothing is known about prenatal hormonal effects on other cognitive abilities, especially those that show a female advantage, because the sex differences are small to moderate, and it has been hard to accrue large enough samples.

8.2.1. Evidence from CAH

Females with CAH have been found to have higher spatial ability than their sisters in childhood, adolescence, and adulthood [72,81,121,136], with a meta-analysis suggesting that the effect is small to moderate [131]. The relatively small size of the effect may explain why the effect is not always seen (e.g., [81]).

8.2.2. Evidence from other clinical conditions

Confirming evidence for androgen effects on spatial ability come from individuals at the other end of androgen levels: males with low early androgen levels due to idiopathic hypogonadotropic hypogonadism (IHH) have lower spatial ability than controls [78]. Importantly, the external genitals of males with IHH appear typical, suggesting that enhanced spatial ability in females with CAH is not due to social responses to their genitals.

8.2.3. Evidence from typical samples

There are now several studies of androgen effects on spatial ability in typical samples that provide converging evidence for prenatal androgen effects on spatial ability. In three studies of opposite-sex twins, females with a male co-twin have been shown to have higher spatial ability than females with a female co-twin [36,75,163]. But, prenatal hormone influences are confounded with postnatal socialization in these findings; females with a male co-twin are reared with a male sibling of the same age. In one study of amniotic hormones, 7-year-old girls who had high levels of amniotic testosterone had better spatial ability than girls who had low levels, but the difference was not found on accuracy, and was seen only on a measure of speed of rotation and only in girls who showed evidence of using a mental rotation strategy [67].

8.3. Pubertal hormone effects on cognition

There has been considerable interest in the idea that pubertal hormones are important for sex differences in spatial ability. The interest stems from two sources. First, the sex difference appears to increase at puberty [20]. Second, work going back more than 30 years ago linked pubertal timing to patterns of cognitive abilities.

8.3.1. Declining sensitivity: effects of timing

In 1976, Waber [164] proposed and confirmed that cognitive sex differences could be explained by maturation rate: late maturers had better spatial than verbal ability, and early maturers the reverse pattern; the effect was partly mediated by the development of hemispheric specialization. Thus, girls' earlier maturation relative to boys was seen to account for their relatively worse spatial and relatively better verbal abilities; that is, maturation was suggested to account for cognitive sex differences. There were several studies following up on Waber's initial findings, with some replicating her effects and some failing to do so; this includes studies of typical adolescents and those with disorders of pubertal development (for review, see [98]). It is likely that inconsistencies reflect low statistical power to see what are likely small effects, but the inconsistencies reduced interest in this topic, so there has been no recent work on it.

8.3.2. Trigger for normative change

Clinical samples provide limited but suggestive evidence of postnatal effects on sex-typed cognitive abilities. First, as noted above, males with low early androgen levels due to IHH have lower spatial ability than controls; their ability is also lower than males with a form of the disorder acquired in adulthood [78]. A difficulty in interpreting results from IHH concerns uncertainty about the timing of the androgen deficiency (i.e., whether it starts in the early postnatal period or not until adolescence). Second, in a study mentioned above showing enhanced spatial ability in females with CAH, ability was highest in those who had advanced bone age in childhood, reflecting continuing postnatal exposure to androgens [121]; it is unclear whether timing of exposure mattered.

Data from a study of hormone treatment for children with delayed puberty do not provide compelling evidence of hormonal influences on spatial ability. Performance on several spatial tests did not vary with hormone treatment or with levels of circulating sex hormones [98]. It is important to note, however, that limitations in the study (e.g., small sample, a relatively late point in puberty) may have made it difficult to see effects. Further, there was no consideration of the cognitive effects of timing of hormone treatment.

8.4. Summary: organizational effects on sex-typed cognition

There has been considerable study of hormonal influences on sex-typed cognitive abilities, but many questions remain. There

is reasonably good evidence that spatial abilities are influenced by prenatal androgens, but the effect is not large and is likely to be moderated by other factors, such as social experiences. There is insufficient information regarding prenatal androgen effects on other cognitive abilities. There is some suggestion that spatial and verbal abilities are influenced by the timing of exposure to pubertal hormones, but the effect is likely small and therefore is moderated by other factors that require explication.

9. Sex-typed behavior problems: evidence for organizational hormonal effects

9.1. Sex differences in behavior problems and psychopathology

Many types of serious behavior problems and mental illness occur at different rates in the two sexes. In general, internalizing disorders (such as anxiety and depression) are more common in girls and women than in boys and men, whereas externalizing disorders (such as conduct disorder, antisocial behavior, and attention-deficit hyperactivity disorder) are more common in boys and men than in girls and women. [170]; boys are also more likely than girls to have learning and reading disabilities [20]. There are important points about the development of sex-differential psychopathology that are relevant to evaluating hormonal influences. First, in childhood, boys have more disorders than do girls; in adolescence and adulthood, girls and women have more disorders than do boys and men [73]. Some of this reflects the types of diagnoses made at different ages. Most childhood disorders (such as attention-deficit hyperactivity disorder, conduct disorder, autism, and reading disabilities) are not diagnosed or treated in adults; many mood disorders (such as anxiety and depression) are not often recognized in children [20]. Second, there is a pronounced female preponderance of depression that begins at puberty; across the adolescent transition, the rates of depression stay the same in boys but increase dramatically in girls [124]. Third, substance use disorders increase in adolescence, with boys having higher rates than girls [65].

Explanations for sex-differential behavior problems include socialization and sex hormones [38]. Most hypotheses about hormonal influences propose that early organizational hormones contribute to the male vulnerability for childhood disorders (e.g., [8,102]), and activational hormones at puberty trigger the female vulnerability to depression and eating disorders [38,102], but there has been recent focus on the importance of organizational hormones at puberty in emerging sex-differential problems in adolescence [54,132,145]. There has been little consideration of the ways that different disorders would be affected by hormones. For example, autism has been claimed to reflect "the extreme male brain" and therefore result from exposure to high prenatal androgens [8], but many other disorders show similar male predominance, and have been suggested by others to also result from high prenatal androgens (e.g., [102]).

9.2. Prenatal hormone effects on behavior problems

It has been difficult to test whether prenatal hormones influence behavior problems because sample sizes are not large enough to detect changes in conditions with relatively low incidence. For example, there are rarely more than 50 girls and women with CAH in any study, and often much less than that; studies of amniotic hormones also have small samples and even more restriction in hormone levels. This means that many studies in these areas have methodological limitations.

9.2.1. Evidence from CAH and other conditions

Early studies of females with CAH focused on learning disabilities, and were methodologically not rigorous. In general, there is no evidence of increased learning disabilities in children with CAH [13]. A recent small-sample study of reading disability suggested an increased incidence in girls with CAH [87] but cautious interpretation is warranted because the comparison group was inadequate, and there was more variability in test scores in girls with CAH than in controls.

Other work has focused on autism, but the low incidence of autism has led researchers to examine "autistic-like" traits rather than the disorder itself. Females with CAH were found to differ from unaffected females on a questionnaire measure of these characteristics, including the total score and subscales of social skills and imagination [94]. It is important to note, however, that low social skills and high imagination are not equivalent to autism. There are several other caveats to interpretation. First, girls and women have better social skills than boys and men, so females with CAH might be expected to have worse social skills than unaffected females because androgen affects these skills within the general population, and not because androgen increases risk for autism or autism-spectrum characteristics. Second, females with CAH scored lower than control females on another characteristic stated to be related to autism, attention to detail; this difference argues against androgen effects on autism, but is consistent with females' higher scores on measures of attention to detail.

There is also some evidence of prenatal androgen effects on aggression, although this is not necessarily disruptive behavior. Females with CAH appear to be more aggressive than their sisters [18,104,128]. Evidence from another condition confirms effects on aggression of early masculinizing hormones: girls prenatally exposed *in utero* to androgenizing progestins because their mothers took the hormones to prevent miscarriage were more likely than their unexposed sisters to report that they would use aggression in a conflict situation [134].

9.2.2. Evidence from typical samples

Amniotic testosterone has been linked to "autistic-like" traits, in several studies from the same lab and possibly from the same sample [4]. But, as with the data on females with CAH, it is unclear whether the characteristics measured really reflect autism or social and cognitive skills that show sex differences.

Markers of prenatal testosterone have been linked to ADHD and related characteristics in some reports (reviewed in [102]). But, cautious interpretation is needed because links have primarily been found only in boys, behavioral measures were often characteristics linked to ADHD and not necessarily diagnoses, and the evidence is based on markers that are not good indicators of within-sex variability in androgens (as noted in Section 3.1.2).

It is also difficult to know how to reconcile findings of links between prenatal testosterone and autism on one hand and ADHD on the other hand. It is unclear when prenatal androgen excess would lead to autism versus ADHD versus other childhood disorders that also show male predominance (such as conduct disorder). It is possible that androgen triggers a genetic vulnerability but this needs to be explicitly considered and tested.

9.3. Pubertal hormone effects on behavior problems

There is considerable interest in the effects of pubertal hormones on behavior problems that begin in adolescence, including those with female predominance (e.g., depression, eating disorders) and those with male predominance (e.g., substance use, delinquency). This work is concerned with direct effects of pubertal hormones on genes and neural systems subserving the balance between appetitive and control systems, affect dysregulation, and heightened stress responsivity (e.g., [1,22,54,102,151]). There is much speculation – and the beginnings of some data – about the ways in which hormones at puberty change the brain in ways that

contribute to both normative changes in adolescence and the development of psychopathology.

9.3.1. Declining sensitivity: effects of timing

There is one study of psychiatric problems in boys with a rare form of precocious puberty, called familial male precocious puberty (FMPP), that has an onset in early childhood [120]. These children could provide an excellent test of declining sensitivity of hormones because they experience a hormone surge early in life, and there is variation in age at onset and treatment. The most notable finding of the study was a high rate of ADHD in these boys, which did not vary with age at diagnosis or treatment modality. Cautious interpretation is needed because the sample was highly selected and rates of ADHD were compared to the general population, rather than an internal comparison group; it is also possible that behavioral change was not in ADHD itself, but in features associated with the disorder (e.g., arousal, irritability) that might reflect activational effects of continuing high androgen levels even with treatment.

There are also a few studies of psychological function in girls with precocious puberty [27,46]. The girls have generally not been found to have psychological problems, and their psychological functioning appears to be unchanged with GnRHa treatment. But, most studies have small samples, imperfect controls, and inadequate measures. Thus, it is difficult to use existing studies to make inferences about whether puberty is a period of declining sensitivity.

Most studies of the consequences associated with variations in pubertal timing have focused on behavior problems in typical youth. The evidence (reviewed in [58,157]) is clearer and more consistent for girls than for boys, perhaps because pubertal onset is more easily marked in girls (by menarche) than in boys. Among girls, early maturers are at increased risk for emotional distress (e.g., depression) and problem behavior (e.g., delinquency, substance use, early sexuality) compared to on-time peers. Among boys, late maturers have low self-esteem compared to on-time peers, whereas early maturers are more popular and have better self-image but are more likely to engage in problem behaviors. Some effects have been shown to be mediated and moderated by social context, especially among girls (reviewed in [157]). For example, the effects of early maturation on substance use in girls may be moderated by parental monitoring [100,168] and mediated by association with deviant peers [101,168]; problem behaviors were higher in early-maturing girls who attended coeducational schools than in those in all-girls' schools [32].

If these psychological effects of variations in timing of exposure to pubertal hormones reflect organizational effects, then they should be permanent. The few studies of the adult consequences of variations in pubertal timing generally show few long-term effects: women who were early maturers are generally similar to women who had on-time development. Early maturation does appear to be associated with lower educational outcome in adulthood, probably as a result of early sexual activity [88] and perhaps with long-term increases in depression [37] but this is not always found [63].

9.3.2. Trigger for normative change

There is some evidence that hormones at puberty trigger sex-linked psychopathology in vulnerable individuals. First, the sex difference in depression that emerges in adolescence appears to result, in part, from hormonal increases at pubertal onset increasing risk for serious depression in girls, especially for those with genetic vulnerability [1,2]. Relatedly, puberty may moderate the manifestation of genetic vulnerability: common genes appear to influence anxiety before puberty and depression after puberty [147]. Second, eating disorders in adolescence appear to be influenced by genes that are triggered at puberty: a longitudinal study showed that genetic factors accounted for a small proportion of the variation in disordered eating at age 11, but almost half the variation at ages 14 and 18 years, and the authors suggested that "the transition from early to mid-adolescence (is) a critical time for the emergence of a genetic diathesis for disordered eating" ([92], p. 1409). Further work suggested that the estradiol surge was the trigger: a measure of mid-pubertal development moderated heritability [39], but age at menarche did not, and heritability was substantial in girls with high estradiol but not in those with low estradiol [93]. It is unclear, however, whether continued high levels of estradiol are necessary to maintain eating disorders or depression.

Aggression appears to be associated with increased hormones at puberty, particularly testosterone in boys (reviewed in [26,157]). But, it is unclear whether this reflects activational or organizational effects. Further, hormones both affect and are affected by behavior, and behavioral effects of testosterone depend on social context. For example, testosterone increased in adolescent male ice hockey players after a victory, but the increase was greater for victories at home compared to victories away [30].

In a study involving hormone treatment for children with delayed puberty, increased physical aggression was associated with estrogen treatment in girls and testosterone treatment in boys [53]. No information was available about associations between aggression and age of treatment initiation, or of long-term effects. Hormone treatment had little effect on other behavior problems (attention, somatic complaints, delinquency, anxiety/depression, social or thought impairments), either in girls or in boys, except for an increase in withdrawn behavior in girls treated with low doses of estrogen [158].

Recent work on puberty as a trigger for normative change has converged on the idea of "dual systems" that underlie risk-taking in adolescence, and that lead to externalizing problems that are more common in boys than in girls [59,154]. The first part of the system, reward- or sensation-seeking, has been shown to increase in early adolescence and then decline through early adulthood; some data show it to be related to pubertal status, at least in boys [155]. There are several suggestions regarding the neural underpinnings of this system, including limbic and paralimbic dopaminergic pathways [153] and immature connections between limbic and prefrontal regions, which make reward-seeking particularly sensitive to social influences [21,40]. The second part of the risk-taking system, impulsivity, declines or remains stable throughout adolescence and early adulthood [154], and is unrelated to pubertal status [155]. Impulse control is hypothesized to be subserved by the prefrontal cortex, so that risk taking persists until neural connections between the (para)limbic subcortical structures and prefrontal cortex are fully developed (in early to middle adulthood) [153].

9.4. Summary: organizational effects on sex-typed behavior problems

There are many speculations about hormonal influences on behavior problems, particularly regarding prenatal androgen effects on childhood problems that are more common in boys than in girls, and pubertal hormone effects on problems that emerge in adolescence. The evidence showing prenatal androgen effects on childhood problems is weak, coming primarily from studies on characteristics related to the problems and not the problems themselves, or from inferred markers of androgen exposure. The evidence for pubertal hormone effects on problems that emerge in adulthood is intriguing, suggesting a role for estradiol in triggering depression and eating disorders in vulnerable girls, and perhaps testosterone in triggering aggression. But, it is unclear whether these effects reflect organizational or activational effects.

There is a large focus, with some data, on differential development of appetitive and cognitive control systems, with the former under the influence of sex hormones and the latter influenced by chronological age. There is little evidence that puberty is a period of declining sensitivity for behavior problems: the psychological consequences of early puberty appear to be limited to adolescence (until peers catch up), although this requires further study.

10. Integrating findings

10.1. Associations among hormonally-influenced characteristics

Among typical individuals, associations among many aspects of sex-typing are not strong [138]. But there are some notable exceptions: people with sex-atypical gender identity and sexual orientation tend to have sex-atypical interests [7]. Similar associations are seen in individuals with atypical hormone exposure. For example, among women with CAH, sexual orientation, satisfaction with gender, and activity interests are correlated (e.g., [80]). But, the cause of those correlations is unclear: does one lead to the other, or do they all reflect a common cause (degree of prenatal androgen exposure). Preliminary data from our lab suggest a cascade model of sex-typed characteristics in females with CAH, with sexual orientation following from activity engagement but preceding gender identity [11]; the results are consistent with a continuum of behavioral effects of prenatal androgen (decreasing effects from activity interests through sexual orientation to gender identity) and with data reported above suggesting that gender identity development continues into adolescence.

10.2. Neural substrates of hormonal influences on behavior

The evidence we reviewed shows that hormones have organizational effects on behavior, with some differences across behaviors in the nature and magnitude of the effects. There is much less known about the neural mediators of those effects.

10.2.1. Sex differences in the brain

There is a long and sometimes checkered history of seeking sex differences in the brain, some of it used to justify women's inferior status in society [146]. Even today, there are some simplistic approaches to studying and interpreting brain sex differences (e.g., [51,70]). But, there are many opportunities. The widespread use of brain imaging techniques has resulted in a considerable literature documenting sex differences in the size of particular brain regions (usually measured with structural magnetic resonance imaging, MRI) and the activity of specific regions during performance of a specific cognitive or emotional task (usually measured with functional MRI, fMRI). This work is reviewed elsewhere (e.g., [60,71,97,135]). It is unclear, however, how to interpret sex differences in the size of specific areas: Brain sex differences are generally small; a large brain size does not always mean optimal function; brain size differences have seldom been explicitly related to behavioral differences; and brain structure changes in response to experience. Thus, even if reliable sex differences in brain structure emerge, it is not clear how they relate to behavior. This issue has also been raised in understanding brain sex differences in other species (e.g., [42]). Further, there is little direct evidence about the ways in which these sex differences are influenced by sex hormones during prenatal and pubertal development (or by sex-related social experiences), and the data that exist are not easy to interpret.

There is much research currently focused on developmental changes in brain structure, including sex differences, particularly at adolescence (reviewed in [96]). Girls appear to reach a peak earlier in development than boys. In the cerebral cortex, the volume appears to peak at age 10.5 in girls and age 14.5 in boys. Gray matter increases and then decreases in both sexes, with the peak occurring 1–2 years earlier in girls than in boys. White matter increases in both sexes throughout ages 3–27, but boys have a steeper rate of increase during adolescence. These data suggest that the key brain sex differences occur in developmental trajectory, rather than in final endpoints. A key question concerns the extent to which these sex differences – and those that are likely to develop earlier – are driven by hormones during critical periods of development. The little we know about the neural effects of early hormones comes from natural experiments. There is much current ongoing work focused on the ways in which pubertal hormones drive sex differences in brain trajectories.

10.2.2. Androgens and the brain

There are two sets of intriguing imaging studies concerning androgen effects on the brain. The first type (from a single group of investigators) focused on brain structure and function in two groups of individuals with androgen excess occurring at different points in development: females with CAH and males with FMPP. Both boys and girls with CAH were found to have smaller amygdala volume than sex- and age-matched controls, but no other differences in brain structure [110]; another (overlapping) sample of females with CAH showed increased amygdala activation to negative facial emotions compared to typical females [50]. Interpretation is not straightforward, however, for several reasons: Increased amygdala activation could relate to reduced volume; the amygdala is not clearly related to the psychological characteristics that most characterize females with CAH; and parallel findings in boys and girls with CAH suggest that some changes in the amygdala reflect effects of cortisol rather than androgen.

Boys with FMPP showed differential hippocampal (but not amygdala) activation to fearful faces relative to baseline, but controls showed no differences [118]. But, boys with FMPP also responded faster than controls to the fearful faces, confounding interpretation of the activation data. Boys with FMPP also had larger gray matter volume in parahippocampal and fusiform gyri and putamen, and smaller precental gyrus relative to controls. Among boys with FMPP, age was positively associated with putamen volume, and testosterone levels were negatively associated with striatum volume [119]. The findings were interpreted to suggest a role for androgen on the development of childhood disorders with male predominance, but the lack of parallel findings in females with CAH reduces the effectiveness of this argument; further, these regions are not the ones most likely to be involved in the characteristics shown to be influenced by androgens (as discussed in Sections 5–9), although they do have a concentration of androgen receptors. It is possible, however, that some of the findings in boys with FMPP have implications for adolescent-onset disorders, given that pubertal rises in testosterone levels have been linked to increases in amygdala and hippocampal volume [25,123].

The second type of study of androgen effects on the brain concerns brain changes in adolescence in relation to androgen exposure measured by genetic variation in the androgen receptor gene. In cortical areas important for cognition, brain development was found to be faster in the sex that usually performs worse in that domain, and androgen responsivity was linked to "masculinization" of adolescent cortical maturation [132]. Androgen responsivity was also found to mediate the link between pubertal testosterone and white matter volume in boys, leading to speculation that androgens indirectly influence white matter development by increasing axonal diameter [129].

10.2.3. Adolescent brain changes

Several ongoing studies are focused specifically on the ways in which adolescent brain development is driven by pubertal hor-

mones, with data just beginning to appear. In one study, for example, brain changes in regions with high sex steroid hormone receptor densities were shown to depend on both sex and puberty: sex differences in the right hippocampus, bilateral amygdala, and cortical gray matter were greater in more sexually mature adolescents [25].

Neural evidence supporting the dual systems underlying the increased risk-taking in adolescence comes from recent data showing that different brain regions have different developmental trajectories in adolescence (discussed in [21,31,40,55,82,96]). The prefrontal cortex continues to develop linearly throughout adolescence, along with the cognitive control functions it subserves. The prefrontal cortex is one of the last brain regions to show the pruning that is characteristic of the brain (gray matter develops in an inverted-U shaped trajectory, with cells proliferating in infancy and early childhood and then undergoing pruning in adolescence). As noted above, there are sex differences in gray matter maturation. Subcortical limbic structures, which are active in affective arousal and impulsivity, mature earlier than prefrontal cortex, purportedly under the influence of pubertal hormones. Because white matter development continues linearly throughout adolescence, and limbic and prefrontal regions have different maturational trajectories, functional and structural connectivity between them is lacking throughout much of adolescence. Thus, "in emotionally salient situations, the limbic system will win over control systems given its maturity relative to the prefrontal control system" ([31], p. 64).

11. Summary, synthesis, and suggestions for future research

There is now considerable work investigating hormonal influences on human behavior, although there is more evidence on some characteristics than on others, and on some types of hormone action than others. In particular, most evidence concerns effects of prenatal androgens studied in females with CAH, although there is increasing evidence from typical samples, especially from amniotic hormones examined in relation to childhood behavior (and probably eventually adolescent and adult behavior). We conclude with a summary of what is known and the kinds of studies that are needed. Table 2 summarizes the evidence on hormonal influences on the characteristics discussed, along with the size of the effects, the source of the evidence, and the strength of the evidence. As is apparent, there is a relative paucity of evidence regarding organizational effects of pubertal hormones, but this is probably not surprising because puberty has only recently been suggested as an organizational period.

11.1. Prenatal effects

There is compelling evidence that prenatal androgens have large masculinizing effects on activity, leisure, and occupational interests across the life span. The initial evidence from females with CAH has been confirmed in other clinical samples and recently in typical samples. There are some failures to find effects in typical samples, probably as a result of low statistical power associated with small samples. It is important to continue to study this issue in typical samples to determine whether androgens masculinize interests in a linear way across the whole range of androgen exposure (with small increases in androgen associated with small increases in male-typed interests), or if androgens lead to masculinized interests only above a threshold of moderately high levels. This question is important for understanding sex differences in career choices, in light of evidence showing that women's underrepresentation in science and math is partly influenced by their interests (e.g., [45]).

There is also good evidence for androgen effects on other characteristics. Prenatal androgens increase sexual arousal to women, but the effect is only moderate in size. For example, about one-third of women with CAH are not exclusively heterosexual, with some variation among women with CAH due to degree of prenatal androgen exposure, but much of the variation still unexplained. But, prenatal androgens appear to have smaller effects on gender identity than on other characteristics. Despite a few well-publicized cases, the systematic evidence suggests that gender identity is better predicted by rearing sex than by prenatal androgen exposure.

There is weaker evidence for prenatal androgen effects on other aspects of sex-typed behavior. Some aspects of behavior problems (aggression, autistic-like features) and cognition (spatial abilities) appear to be masculinized by prenatal androgens to a moderate degree. But, there is a need for more evidence, especially from typical samples, and to understand factors that modify androgen effects on these characteristics. For example, it will be interesting

Table 2
Summary of organizational hormone effects on sex-typed behavior.

	Prenatal hormones				Pubertal hormones			
	Effect		Evidence		Effect		Evidence	
	A/E	Size	Source	Strength	A/E	Size	Source	Strength
Activity interests	A	Large	NatExp	+++				
			Typ	++				
Gender identity	A	Small-moderate	NatExp	+++	A♂	Moderate	NatExp	++
					E♀		GID	++
Sexual orientation	A	Moderate	NatExp	+++				
Cognition: spatial abilities	A	Small-moderate	NatExp	++	A	Moderate	NatExp	+
Behavior problems: autism	A	Moderate	NatExp	+				
			Typ	+				
Childhood ADHD	A	Small	Typ	+	A	Moderate	NatExp	+
Adolescent depression					E♀	Moderate	Typ	++
Eating disorders					E♀	Moderate	Typ	++

Effect
A/E: hormone responsible; A: androgens; E: estrogens
Size: effect size

Evidence
Source (of evidence): NatExp: natural experiments; Typ: typical samples; GID: gender identity disorder
Strength (of evidence): + weak; ++ moderate; +++ strong.

to know how spatial experiences interact with prenatal androgen exposure to affect spatial ability.

It will also be very interesting to study behavior in females with CAH who receive prenatal treatment with dexamethasone. Treatment is intended to prevent the virilization of the genitalia and is generally successful if started early in gestation. Treatment should also prevent masculinization of the brain and behavior, and therefore females with CAH prenatally treated with dexamethasone should be similar to typical females and less masculine than females with CAH who were not treated prenatally.

11.2. Pubertal effects

There is currently little direct evidence for permanent effects of pubertal hormones, but it is likely that this situation will improve in the near future, because much work is focused on the ways that pubertal hormones trigger genetic risk for depression and eating disorders, and the appetitive system that contributes to risk-taking. The existing evidence suggests that organizational effects in puberty are driven, at least in part, by estrogens in girls and androgens in boys. The evidence to date is more supportive of the notion that puberty is a separate organizational period (Fig. 1, top panel) than that it represents a period of declining sensitivity. Studies of normal variations in pubertal timing suggest that the psychological consequences are short-lived, and that the main long-lasting effect occurs through increased early sexual activity, probably not an organizational effect. But, it is important to explore this issue further.

The most intriguing evidence for effects of pubertal hormones concerns gender identity. Individuals with 5α-reductase deficiency reared as females are more likely than not to change gender in adolescence when they experience a surge of androgens. Children with gender identity disorder have high rates of desistance after puberty. It is surprising that gender identity may still be forming in adolescence, because its early development is a key part of many theories and it has been hypothesized to serve as a trigger for gender development [138]. And, of course, it is not clear if behavioral change is due to direct hormone effects on the brain or responses to physical changes. But, this is an exciting area for future research, and it will be important to have additional evidence to confirm or refute the existing data, to elucidate mechanisms of change, and to see how the actions of pubertal hormones depend on actions of prenatal hormones.

There are a number of opportunities for studying behavioral effects of pubertal hormones that are yet to be fully exploited. These include variations in pubertal timing, pubertal disorders and variations in timing of hormone replacement, endocrine disorders with onset in puberty and treatment at a later point, and hormone treatment of children with gender identity disorder. In order to establish that hormones affect behavior through permanent changes to the brain, such studies need to involve follow-up of participants into adulthood. As noted above, studies of normal variations in pubertal timing suggest that the psychological consequences are short-lived, and therefore not likely a reflection of organizational hormones. But, there may well be other organizational effects of pubertal hormones that have yet to be revealed.

11.3. Conclusions

There is now little question that hormones exert permanent and powerful effects on human sex-typed behavior. There has been much more research on prenatal than pubertal hormone effects, so it is not surprising that there is less evidence for puberty as an organizational period compared to the prenatal period. But, there are many remaining questions about both periods, including the neural substrates for hormone effects, reasons for the variability in the size of the effects across behaviors, and relation between prenatal and pubertal effects. We look forward to the answers to those questions.

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